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**BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES**

Application Number: 10/553,869
Filing Date: October 21, 2005
Appellant(s): LORENTSEN ET AL.

Patrick Gattari
For Appellant

**EXAMINER'S ANSWER**

This is in response to the corrected appeal brief filed April 5, 2011, appealing from the Office Actions mailed June 14, 2010 and February 10, 2011.

**(1) Real Party in Interest**

The Examiner has no comment on the statement, or lack of statement, identifying by name the real party in interest in the brief.

**(2) Related Appeals and Interferences**

The Examiner is unaware of any related appeals, interferences, and judicial proceedings which may be related to, directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

**(3) Status of Claims**

The following is a list of claims that are rejected and pending in the application:

Claims 1, 4, 6, 8-11, 13-17, 40, 41, and 43-51.

**(4) Status of Amendments After Final**

The Examiner has no comment on the Appellant's statement of the status of amendments after final rejection contained in the brief.

**(5) Summary of Claimed Subject Matter**

Regarding the summary of claimed subject matter contained in the brief, the Examiner makes the following comments. The claims under appeal recite the phrase "authentic form", the definition of which forms the basis for much of the argument presented by Appellants. Thus, the following comments are made.

The specification provides the following statements regarding the phrase "authentic form" (paragraph bridging pg 6-7):

"In accordance with the present invention there is provided a method for producing polypeptides of interest in authentic form. As used herein, the term "authentic form" refers to a polypeptide which comprises the amino acid sequence thereof without any additional amino acid

residues. As described above, a major problem associated with several of the presently applied enzymes for fusion protein cleavage is that spurious or extraneous amino acids frequently remains attached to the cleaved polypeptide product, i.e. resulting in a polypeptide which is not in an "authentic form". Thus, in the present context the polypeptide of interest in authentic form refers to a polypeptide having the same primary amino acid sequence as that encoded by the native gene sequence coding for the polypeptide of interest, i.e. it does not contain any non-native amino acids. The term "native gene sequence" is not necessarily a gene sequence that occurs in nature, but it may also be partly or completely artificial. Likewise it will be appreciated that a polypeptide of interest in authentic form not necessarily is a polypeptide that occurs in nature, but it may also be partially or completely artificial. In contrast, a "non-authentic" polypeptide contains at least one amino acid which is not encoded for by the native gene sequence coding for the polypeptide of interest."

Said statements define the phrase "authentic form" as encompassing recombinant proteins encoded by recombinant nucleic acid molecules. Said recombinant proteins include those that have been modified to include any number of deletions, substitutions, and additions, including additions at the N- and C-terminus, but do not comprise additional, "non-authentic", amino acids from a proteinase cleavage motif.

However, said recombinant proteins do include proteins in "authentic form" that comprise, at the N- or C-terminus, "authentic amino acids" of the "authentic protein" that are also part of a proteinase cleavage motif. The following is a cartoon representing this latter type of recombinant protein, wherein the amino acids (motif) represent the protease cleavage motif, the amino acids [ifproteinproteinprotein…..] represent the "authentic protein", and ↓ represents the protease cleavage site. In this cartoon the "if" amino acids are part of both the protease cleavage motif and the "authentic protein".

**(mot↓[if)proteinproteinprotein….]**

**(6) Grounds of Rejection to be Reviewed on Appeal**

The Examiner has the following comments on the Appellant's statement of the grounds of rejection to be reviewed on appeal.

Appellants' statement that Claims 4-6 and 41 are rejected under 35 U.S.C. 103(a) as obvious over Azad et al Harris et al and Casciola-Rosen et al in view of Boutin, et al is **not correct**. It is Claims 4, 6, and 41 that are rejected under 35 U.S.C. 103(a) as obvious over Azad et al Harris et al and Casciola-Rosen et al in view of Boutin, et al.

Every ground of rejection set forth in the Office action from which the appeal is taken (as modified by any advisory action of February 10, 2011) is being maintained by the Examiner.

No grounds of rejection are listed under a subheading "WITHDRAWN REJECTIONS." No New grounds of rejection are presented under a subheading "NEW GROUNDS OF REJECTION."

**(7) Claims Appendix**

The Examiner has no comment on the copy of the appealed claims contained in the Appendix to the Appellant's brief.

**(8) Evidence Relied Upon**

- Azad et al, Large-scale production and characterization of recombinant human immunodeficiency virus type 1 Nef. J Gen Virol. 1994 Mar;75 ( Pt 3):651-5.
- Bleackley et al, Isolation of two cDNA sequences which encode cytotoxic cell proteases. FEBS Lett. 1988 Jul 4;234(1 ):153-9.
- Boutin et al, Myristoylation. Cell Signal. 1997 Jan;9(1):15-35. Review.
- Casciola-Rosen et al "Cleavage by Granzyme B is Strongly Predictive of Autoantigen Status: Implications for Initiation of Autoimmunity", J Exp Med, Vol. 190, No. 6, pg. 815-825, September 20, 1999.

- GE Healthcare pGEX Vectors, GST Gene Fusion System May, 2007; see Exhibit A filed June 8, 2009.
- Harris et al, Definition and Redesign of the Extended Substrate Specificity of Granzyme B, J Biol Chem. 1998 Oct 16; 273(42): 27364-27373.
- Pharmacia, Inc., (1986) Coupling Gels. In: Affinity Chromatography, Principles & Methods. pg 9.
- Sigma, Inc. (1998) Thrombin CleanCleav Kit Recom-T Product Information.
- Wan et al, Autoprocessing: an essential step for the activation of HIV-1 protease. Biochem J. 1996 Jun 1;316 ( Pt 2):569-73.

**(9) Grounds of Rejection**

The following ground(s) of rejection are applicable to the appealed claims:

(1) Claims 1, 9-11, 16, 17, 40, 44-46, 50, and 51 are rejected under 35 U.S.C. 103(a) as being unpatentable over Azad et al, 1994 in view of Harris et al, 1998 and further in view of Casciola-Rosen et al, 1999. Azad et al teaches a GST-nef27 fusion protein (pg 651, parg 2-3), wherein nef27 contains Met-Gly at the N-terminus (pg 651, parg 2, line 7; encoded by "ATG-GGT"). Azad et al does not teach a GST-Granzyme B cleavage motif-nef27 fusion protein or using Granzyme B to release authentic nef27 from such a fusion protein. Harris et al teaches using Granzyme B to cleave fusion proteins comprising the motif IEADXG, wherein X is any amino acid (Fig 5A&D).

It would have been obvious to a person of ordinary skill in the art to modify the fusion protein of Azad et al to incorporate the motif IEAD between the GST fusion partner and nef27. Said fusion protein would have the structure:

**GST-(IEAD↓ [MG)nef27]**

wherein, (IEADMG) is the Granzyme B cleavage motif, [MGnef27] is authentic nef27, ↓ is the Granzyme B cleavage site (Harris et al; Fig 5D), and "MG" is comprised within both the Granzyme B cleavage motif and authentic nef27.

It would have been further obvious to the skilled artisan in the art to cleave said fusion protein with rat Granzyme B (Harris et al). It would have also been obvious to cleave said fusion protein with human Granzyme B, which, as acknowledged by Appellants (February 18, 2009, pg 14, section D) was known in the art and cleaves the motif IEAD↓X (Casciola-Rosen et al; pg 816, parg 2, Table I-Topoisomerase I). Motivation to make the fusion protein and cleave it with Granzyme B derives from the desire to produce authentic nef27, which is critical for development of AIDS (Azad et al; Abstract). It would also have been obvious to adapt the fusion protein rendered obvious by the above teachings to replace the GST fusion partner with a 6X-His fusion partner, which was well-known in the art. Motivation to do so derives from the desire to use Ni/nitrilotriacetic acid resin for purification of the fusion protein, as taught by Harris et al (pg 27366, parg 3). The expectation of success is high, as the making, purification, and cleaving of fusion proteins were all well-known in the art. Therefore, Claims 1, 9-11, 16, 17, 40, 44-46, 50, and 51 are rejected under 35 U.S.C. 103(a) as being unpatentable over Azad et al, 1994 in view of Harris et al, 1998 and further in view of Casciola-Rosen et al, 1999.

(2) Claims 4, 6, and 41 are rejected under 35 U.S.C. 103(a) as being unpatentable over the combination of Azad et al, 1994, Harris et al, 1998, and Casciola-Rosen et al, 1999 in view of Boutin et al, 1997. The teachings of Azad et al, Harris et al, and Casciola-Rosen et al are described above. Said combination does not teach preparing an authentic protein of interest,

wherein the authentic protein of interest is an enzyme. Boutin et al teaches that, like nef27, essentially all proteins that become myristoylated begin with Met-Gly at the N-terminus, including the enzyme calcineurin B (Table 3). It would have been obvious to a person of ordinary skill in the art to modify the method rendered obvious by the combination of Azad et al, Harris et al, and Casciola-Rosen et al, such that the nef27 protein is substituted with calcineurin B. Motivation to do so derives from the desire to produce authentic calcineurin B, a calcium-dependent phosphatase, using Granzyme B. The expectation of success is high, as the making and cleaving of fusion proteins is well-known in the art. Therefore, Claims 4, 6, and 41 are rejected under 35 U.S.C. 103(a) as being unpatentable over the combination of Azad et al, 1994, Harris et al, 1998, and Casciola-Rosen et al, 1999 in view of Boutin et al, 1997.

(3) Claims 13-17 and 47-49 are rejected under 35 U.S.C. 103(a) as being unpatentable over the combination of Azad et al, 1994, Harris et al, 1998, and Casciola-Rosen et al, 1999 in view of Sigma Inc, 1998 or Pharmacia, Inc 1986. The teachings of Azad et al, Harris et al, and Casciola-Rosen et al are described above. Said combination does not teach a method wherein the Granzyme B is immobilized. However, the use of immobilized proteases for generating a polypeptide from a fusion protein is well-known in the art; see, for example Sigma, Inc. In addition, it was well-known that proteins can be immobilized via the N-terminus, the C-terminus, or lysine residues (Pharmacia, Inc). It would have been obvious to a person of ordinary skill in the art to modify the method of rendered obvious by the combination of Azad et al and Harris et al to used immobilized Granzyme B. Motivation to do so derives from the desire to circumvent the need to remove Granzyme B from the generated authentic nef27 polypeptide. The expectation of success is high, as the use of immobilized proteases for cleaving fusion proteins was well-known

in the art. Therefore, Claims 13-17 and 47-49 are herein rejected under 35 U.S.C. 103(a) as being unpatentable over the combination of Azad et al, 1994, Harris et al, 1998, and Casciola-Rosen et al, 1999 in view of Sigma Inc, 1998 or Pharmacia, Inc 1986.

(4) Claims 8 and 43 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wan et al, 1996 in view of Bleackley et al, 1988 and further in view of Harris et al, 1998. Wan et al teaches a method for production of authentic HIV-1 protease, wherein the method uses a fusion protein comprising HIV-1 protease that proteolytically autoprocesses, thereby producing the active authentic HIV-1 protease (pg 572, parg 2; Fig 3). Wan et al does not teach a method for production of authentic Granzyme B protease, wherein the method uses fusion proteins comprising Granzyme B protease that proteolytically autoprocesses, thereby producing the active authentic Granzyme B protease. Bleackley et al teaches that Granzyme B is synthesized as a prepro-form, which must be cleaved, to remove the first 20 amino acids, for activation (pg 155, parg 4). Bleackley et al further teaches that the site of said processing occurs within the motif $^{17}$GAEE↓II$^{22}$ (Fig 1). It would have been obvious to a person of ordinary skill in the art to adapt the method of Wan et al to make a method for producing authentic Granzyme B protease, wherein the method use a fusion protein comprising Granzyme B protease that proteolytically autoprocesses. In said adapted method, the motif GAEE↓II$^{2}$ in Granzyme B would be replaced with the motif IEAD↓IG$^{2}$ which, as taught by Harris et al, is a motif cleaved by Granzyme B (Fig 5). The resulting fusion protein would consist of an N-terminal fusion partner linked to the prepro region of Granzyme B, or a fragment thereof, followed by the IEAD↓IG$^{2}$ Granzyme B cleavage motif, wherein IG$^{2}$ begins the sequence for the authentic active region of Granzyme B, as encompassed by the instant claims. Said fusion protein would proteolytically autoprocess, thereby

producing the active authentic Granzyme B protease. Motivation to make such a method is provided by the desire to produce the active Granzyme B protease and to screen for inhibitors of auto-processing. The expectation of success is high, as the making and autoprocessing of fusion proteins was known in the art. In addition, the skilled artisan would believe that, more likely than not, the Ile>Gly substitution at the penultimate position of Granzyme B would not affect Granzyme B protease activity. Therefore, Claims 8 and 43 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wan et al, 1996 in view of Bleackley et al, 1988 and further in view of Harris et al, 1998.

**(10) Response to Arguments**

(1) Regarding the rejection of Claims 1, 9-11, 16, 17, 40, 44-46, 50, and 51 under 35 U.S.C. 103(a) as being unpatentable over Azad et al, 1994 in view of Harris et al, 1998 and further in view of Casciola-Rosen et al, 1999, Appellants provide the following arguments. These arguments are not found to be persuasive for the reasons following each argument.

(A) A claimed invention is unpatentable if the differences between it and the prior art "are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art." 35 U.S.C. § 103(a); see Graham v. John Deere Co., 383 U.S. 1, 14 (1966). The ultimate determination of whether an invention is or is not obvious is based on underlying factual inquiries including: (1) determining the scope and content of the prior art; (2) ascertaining the differences between the prior art and the claims at issue; (3) resolving the level of ordinary skill in the pertinent art; and (4) evaluating evidence of secondary considerations. See Graham, 383 U.S. at 17-18.

The Supreme Court emphasizes that the key of supporting any rejection under 35 U.S.C. § 103 is the clear articulation of the reason(s) why the claimed invention would have been obvious. KSR Int'l Co. v. Teleflex Inc., 127 U.S. 1727, 1741 (2007). The Court, quoting In re Kahn, stated that "rejections on obviousness cannot be sustained with mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness." Id., citing, In re Kahn, 441, F.3d 977, 988 (Fed. Cir. 2006).

The failure of asserted references to teach or suggest each and every feature of instant claims is fatal to an obviousness rejection under 35 U.S.C. § 103. Section 2143.03 of the MPEP requires the "consideration" of every claim feature in an obviousness determination. To render instant claims unpatentable, however, the Office must do more than merely "consider" each and every feature for this claim. Instead, the asserted references, individually or in combination, even if supported by the motivation to combine, must also teach or suggest each and every claim feature. See In re Royka, 490 F.2d 981,180 USPQ 580 (CCPA 1974) (to establish prima facie obviousness of a claimed invention, all the claim features must be taught or suggested by the prior art).

The Federal Circuit recently reiterated that in order to support a conclusion of obviousness, the combined prior art must teach all of the elements of the claimed invention. Honeywell Int'l Inc. v. United States, 609 F.3d 1292, 95 U.S.P.Q.2d 1193 (fed. (St. 2010). See also In re Wada and Murphy, Appeal 2007-3733, citing In re Ochiai, 71 F.3d 1565, 1572 (Fed. Cir. 1995) (a proper obviousness determination requires that an Examiner make "a searching comparison of the claimed invention - including all its limitations - with the teaching of the prior art."

Further, the necessary presence of all claim features is axiomatic, since the Supreme Court has long held that obviousness is a question of law based on underlying factual inquiries, including ... ascertaining the differences between the claimed invention and the prior art. Graham v. John Deere Co., 383 U.S. 1,148 USPQ 459 (1966). MPEP § 2143 requires that the prior art provide at least a suggestion of all of the features of a claim in the prior art. This suggestion should serve as the foundation of an "articulated reasoning with some rational underpinning to support the legal conclusion of obviousness." KSR Int 'I v. Teleflex Inc., 127 S. Ct. 1727, 1741 (2007) (quoting In re Kahn, 441 F.3d 977, 988 (Fed. Cir. 2006).

(A) Reply: Appellants' review of the basis for a rejection under 35 USC 103(a) is acknowledged.

(B) In the Office Action mailed June 14, 2010 (pg 5), the Examiner sets forth the following fictitious examples of polypeptides, described as "the fusion proteins to be used in the methods rendered obvious by the combination of Azad, et al, Harris et al and Casciola-Rosen et al:"

GST-IEAD↓[N-Met-Gly-nef27-C]

HIS6x-IEAD↓[N-Met-Gly-nef27-C]

wherein GST and HIS6x are fusion partners, [N-Met-Gly-nef27-C] is the authentic sequence for nef27, IEAD is a cleavage motif for Granzyme B, and ↓ indicates the cleavage position for Granzyme B.

These examples of fusion proteins are simply the creativity of the Examiner, and not found anywhere in the prior art. None of the cited references teach or suggest the production of a polypeptide in authentic form. Indeed, the Office Action even acknowledges that Azad, et al, which the Examiner uses for the reference to nef27, "does not teach the production of a

polypeptide of interest in authentic form." (pg 8, last parg). While acknowledging the deficiency in the prior art to teach this essential feature of the claims, the Examiner asserts that it is the combination of the references that renders the claimed invention obvious. The Examiner's conclusion, however, is completely inconsistent with the Examiner's acknowledgement that the prior art does not teach "the production of a polypeptide of interest in authentic form."

(B) Reply: It is acknowledged that no single reference teaches the fusion proteins set forth above. If any single reference did teach said fusion proteins and cleavage thereof with Granzyme B, this would be a rejection under 35 USC 102, not 35 USC 103(a).

(C) Also, the Examiner is not correct in describing [N-Met-Gly-nef27-C] as the "authentic sequence for nef27."

(C) Reply: Appellants have asserted that the protein used by Azad et al, having an N-terminal Met-Gly dipeptide, (pg 651, parg2, line 7; encoded by "ATG-GGT") is not the authentic sequence for nef27. However, Appellants have failed to provide evidence to support said assertion or to direct the Office to any sequence they believe to be the authentic sequence for nef27.

(D) The definition of authentic form in the specification is clear: "authentic form" refers to a polypeptide that has "no extraneous amino acids derived from the cleavage site." (pg. 5, lines 5-7). Therefore, the polypeptide of interest in authentic form refers to a polypeptide having the same primary amino acid sequence as that encoded by the gene sequence coding for the polypeptide of interest; i.e., it does not contain any non-native amino acids (Id., pg 6, line 24 – pg 7, line 2). As a point of clarification, the specification also describes that in the claimed invention, a polypeptide of interest in authentic form is not always a polypeptide that occurs in nature, but it may also be partially or completely artificial (pg 7, lines 3-7). Not only does the prior art failed to teach the

production of a polypeptide of interest in authentic form, the art also fails to teach a polypeptide of interest in authentic form adjacent to the Granzyme B cleavage site as recited in independent claims 1 and 40.

(D) Reply: As explained above (section (5) Summary of Claimed Subject Matter), the specification provides the following statements regarding the phrase "authentic form" (paragraph bridging pg 6-7):

"In accordance with the present invention there is provided a method for producing polypeptides of interest in authentic form. As used herein, the term "authentic form" refers to a polypeptide which comprises the amino acid sequence thereof without any additional amino acid residues. As described above, a major problem associated with several of the presently applied enzymes for fusion protein cleavage is that spurious or extraneous amino acids frequently remains attached to the cleaved polypeptide product, i.e. resulting in a polypeptide which is not in an "authentic form". Thus, in the present context the polypeptide of interest in authentic form refers to a polypeptide having the same primary amino acid sequence as that encoded by the native gene sequence coding for the polypeptide of interest, i.e. it does not contain any non-native amino acids. The term "native gene sequence" is not necessarily a gene sequence that occurs in nature, but it may also be partly or completely artificial. Likewise it will be appreciated that a polypeptide of interest in authentic form not necessarily is a polypeptide that occurs in nature, but it may also be partially or completely artificial. In contrast, a "non-authentic" polypeptide contains at least one amino acid which is not encoded for by the native gene sequence coding for the polypeptide of interest."

Said statements define the phrase "authentic form" as encompassing recombinant proteins encoded by recombinant nucleic acid molecules. Said recombinant proteins include those that have been modified to include any number of deletions, substitutions, and additions, including additions at the N- and C-terminus, but do not comprise additional, "non-authentic" amino acids derived from the proteinase cleavage motif.

Thus, said recombinant proteins include proteins in "authentic form" that comprise, at the N- or C-terminus, "authentic amino acids" that are part of the desired "authentic protein" and are also part of a proteinase cleavage motif. The following cartoon represents this latter type of

recombinant protein, wherein the amino acids (motif) represent the protease cleavage site, the amino acids [ifproteinproteinprotein.....] represent the "authentic protein", and ↓ represents the protease cleavage site. In this cartoon, the "if" amino acids are part of both the protease cleavage motif and the "authentic protein".

**(mot↓[if)proteinproteinprotein....]**

As acknowledged by Appellants above (B), recombinant proteins rendered obvious by the combination of Azad et al, Harris et al, and Casciola-Rosen et al are:

**GST-IEAD↓[MG-nef27]**

**HIS6x-IEAD↓[MG-nef27-C]**

wherein GST and HIS6x are fusion partners, [MG-nef27] is the authentic sequence for nef27, IEADMG is a cleavage motif for Granzyme B, ↓ indicates the cleavage position for Granzyme B, and the dipeptide Met-Gly are comprised within both the cleavage motif and authentic nef27.

Said recombinant proteins are encompassed by the pattern (mot↓[if)proteinproteinprotein....] and cleavage of said recombinant proteins with Granzyme B results in the production of authentic nef27. Thus, the method rendered obvious by the combination of Azad, et al, Harris et al and Casciola-Rosen, et al is a method for making an authentic polypeptide by cleaving a fusion protein, comprising the authentic polypeptide and a Granzyme B cleavage motif, with Granzyme B to release the authentic polypeptide.

(E) There is no dispute that Harris et al does not teach a polypeptide of interest in authentic form adjacent to a Granzyme B cleavage site. Fig 5 and the remainder of Harris et al teach the cleavage of a fusion protein to produce a pIII coat protein of M13 bacteriophage.

Harris et al discloses a six amino acid motif, IEAD↓AL, that is explained as essential for Granzyme B cleavage (Abstract and Fig 5). The amino acids following the cleavage site, the P1' and P2' amino acids and a linker (AGPGGG), are not part of the authentic polypeptide sequence of the pIII coat protein of M13 bacteriophage, which is the polypeptide of interest in Harris et al See p. 27365, last paragraph of col. 2. Therefore, following cleavage at the cleavage site (↓), the polypeptide of interest is left with two non-authentic peptides (AL) at the N-terminus.

(E) Reply: It is acknowledged that Fig 5 of Harris et al shows the results of Granzyme B cleavage of a series of fusion proteins comprising a fragment of pIII and the motifs set forth by the formula $P^4$[I/V]-[E/Q/M]-[X]-[D]↓[X]-[G]$P^{2'}$.

Harris et al does not disclose that the six amino acid motif, IEAD↓AL is essential for Granzyme B cleavage. Harris et al clearly states: "an optimal substrate for granzyme B that spans over six subsites was determined to be Ile-Glu-Xaa-(Asp↓Xaa)-Gly, with cleavage of the Asp↓Xaa peptide bond" (Abstract). Thus, Harris et al teaches that any motif that fits the pattern IEXDXG, including IEAD↓MG, as recited in the instant rejection, will be cleaved by Granzyme B.

(F) Also, Azad et al does not teach a polypeptide of interest in authentic form adjacent to a cleavage site. In earlier Office Actions, the Examiner refers to p. 651, parg2 of Azad as teaching that a nef27 polypeptide contains Met-Gly at the N-terminus (action of April 7, 2009, pg 6; Advisory Action of June 18, 2009). However, Azad et al teaches the production of the nef27 protein using the pGEX-2T fusion vector described in Azad et al (pg 651, last parg). This vector includes a thrombin recognition sequence and cleavage site in the GST peptide encoded by the vector: Leu-Val-Pro-Arg↓Gly-Ser, wherein "↓" is the thrombin cleavage site. See Ex. A (Evidence Appendix) which is a map of the pGEX-2T vector showing the cleavage site. Therefore, the Nef

protein derived from thrombin-cleaved GST-Nef (pg 653) is left with Gly-Ser from the vector at the N-terminus. Because the Nef peptide produced as described in Azad et al has non-native amino acids left over from the vector (Gly- Ser) at the N-terminus, the authentic nef27 in Azad et al is not adjacent the cleavage site and Azad et al does not teach the production of a polypeptide in authentic form as presently claimed.

(F) Reply: It is acknowledged that Azad et al does not teach Appellants' invention. If Azad et al did so teach, this would be a rejection under 35 USC 102. It is also acknowledged that Azad et al uses the pGEX-2T fusion vector. However, as explained in the rejection above, it would have been obvious to a person of ordinary skill in the art to "modify the fusion protein of Azad et al" to incorporate the motif IEAD between the GST fusion partner and nef27. Said fusion protein would have the structure GST-(IEAD↓ [MG)nef27] wherein, (IEADMG) is the Granzyme B cleavage motif, [MGnef27] is authentic nef27, ↓ is the Granzyme B cleavage site (Harris et al; Fig 5D), and "MG" is comprised within both the Granzyme B cleavage motif and authentic nef27.

(G) (i) In the recent Office Action, the Examiner states that the "teaching of Azad et al regarding the Leu-Val-Pro-Arg↓Gly-Ser motif and cleavage of thrombin are not used for the instant rejection (June 14, 2010, pg 9). Instead, the Examiner states that the "relevant teaching of Azad et al is the generic idea of cleaving a fusion protein comprising nef27 to release nef27 protein." Id. But as addressed above, the nef27 is not in authentic form as presently claimed.

(ii) If the only relevant teaching from Azad et al is a generic teaching of cleaving a fusion protein to produce a non-authentic polypeptide, Azad et al is merely cumulative of Harris et al.

(G) Reply: (i) Reply: See Reply (F), above.

(ii) Reply: Harris et al does not teach use of a fusion protein comprising nef27 to produce any nef27 construct.

(H) With regard to Casciola-Rosen et al, this reference teaches a number of Granzyme B cleavage motifs, but it does not teach cleavage of fusion proteins or the production of a polypeptide in authentic form.

(H) Reply: It is acknowledged that Casciola-Rosen et al does not teach cleavage of fusion proteins; it is Azad et al and Harris et al that teach cleavage of fusion proteins. It is acknowledged that Casciola-Rosen et al does not teach the production of a polypeptide in authentic form. It is the combination of Azad et al, Harris et al, 1998 and Casciola-Rosen et al that teaches production of a polypeptide in authentic form.

(I) Because none of the references teach or suggest the production of the authentic form of polypeptide of interest, the reference can not be combined to render obvious the present invention.

(I) Reply: KSR International vs Teleflex Inc. (Federal Register/Vol. 72, No. 1995, October 10, 2007) takes precedent in the Office's current determination of obviousness under § 103(a). Therein, rationales supporting an obviousness rejection are (72 Fed. Reg. 57526; esp pg 57529):

(a) combining prior art elements according to known methods to yield predictable results,
(b) simple substitution of one known element for another to obtain predictable results,
(c) use of a known technique to improve similar devices (methods or products) in the same way,
(d) applying a known method to a known product or method ready for improvement to yield a predictable result,
(e) "obvious to try" -choosing from a finite number of identified, predictable solutions, with a reasonable expectation of success,
(f) known work in one filed of endeavor may prompt variations for use in the same or a different field, if the variants would have been predictable, and
(g) some teaching, suggestion, or motivation in the prior art to lead the skilled artisan to modify or combine prior art teachings.

Thus, it is not required that one of the references specifically teaches or suggests the recited invention.

In the instant case, the relevant rationales for supporting the obviousness rejection are (a) combining the prior art references will, more likely than not, lead to the predicated result of a method of producing authentic nef27 by cleaving the fusion protein GST-IEAD↓[MG-nef27] or HIS6x-IEAD↓[MG-nef27] with Granzyme B, (b) simple substitution of one known element for another to obtain the above described predictable result, (c) use of a known technique to improve the method of Azad et al by incorporating the teachings of Harris et al and Casciola-Rosen et al, and (g) based on knowledge of the skilled artisan, there would be motivation to combine the teachings of Azad et al, Harris et al, and Casciola-Rosen et al, 1999 to produce authentic nef27.

(J) Harris et al provides no reason for one of ordinary skill in the art to use their method to produce a polypeptide in authentic form as presently being claimed. Indeed, Harris et al teaches away from the present invention because Harris et al teaches the necessity of P1' and P2' amino acids (amino acids that are in the C-terminal direction from the cleavage site).

(J) Reply: Harris et al does not teach away from the instant invention; Harris et al does not teach the necessity of P1' and P2' amino acids.

Harris et al clearly teaches that only a four amino acid sequence, P4-P1, is required for efficient cleavage by Granzyme B (pg 27368, parg1; Table II). Nonetheless, it is acknowledged that Harris et al teaches that an optimal cleavage motif for Granzyme B spans six residues as set forth by IEXD↓XG (Abstract). Said teachings of Harris et al do not teach away from the recited invention because, as stated above, the P1' and P2' amino acids can be provided by the first two amino acid of the authentic polypeptide, which is encompassed by the instant invention.

(K) (i) Instead of teaching or suggesting the production of a polypeptide of interest in authentic form, Harris et al describes the cleavage of a variety of short synthetic amide substrates produced via a combinatorial library (Tables 2&3).

(ii) Harris et al merely identifies a handful of six amino acid sequences and the specific site of Granzyme B cleavage and provides no mention or suggestion to use Granzyme B for the purification of protein of interest in authentic form. To put it another way, using the words of the CAFC in In re O' Farrell, Harris et al. gives one skilled in the art "no indication of which parameters were critical or no direction as to which of many possible choices is likely to be successful" to arrive at the claimed invention. In re O'Farrell, 853 F.2d 894, 895 (Fed. Cir. 1988).

(K) Reply: (i) It is acknowledged that Harris et al describes the cleavage of a variety of short synthetic amide substrates produced via a combinatorial library. However, Harris et al also describes cleavage of fusion proteins with Granzyme B (Fig 5).

(ii) It is acknowledged that Harris et al does not mention or suggest using Granzyme B for the purification of a protein of interest in authentic form. However, as explained in Reply (I), above, the instant rejection does not require that Harris et al so teach.

(L) Moreover, while Casciola-Rosen et al teaches a number of Granzyme B cleavage motifs, it does not teach cleavage of fusion proteins or the production of a polypeptide in authentic form. Thus, Casciola-Rosen et al does not cure the deficiencies of Harris et al and Azad, et al.

(L) Reply: It is acknowledged that Casciola-Rosen et al does not teach cleavage of fusion proteins or the production of a polypeptide in authentic form. It is Azad et al and Harris et al that teach cleavage of fusion proteins and it is the combination of Azad et al, Harris et al, and

Casciola-Rosen et al that teach the production a polypeptide in authentic form, as encompassed by Claims 1, 9-11, 16, 17, 40, 44-46, 50, and 51.

(M) The Examiner has not suggested any motivation to combine any of the references except for the general overall motivation to produce polypeptides in authentic form. While Applicants do not dispute that there is a motivation to make pure, authentic polypeptide, the Examiner has not cited any rational reasoning why a skilled artisan would choose the method of Harris, et al., which the Examiner agrees does not teach the production of a polypeptide of interest in authentic form, to produce a nef27 polypeptide of Azad et al The Examiner states that it would have been obvious to adapt the fusion protein to replace the GST fusion partner with an 6X-His fusion partner of Harris, et al. Even doing so, however, does not render the polypeptide of interest in authentic form because, as explained above, the cleave motif of Harris does not product a polypeptide of interest in authentic form.

As recently reiterated in Bayer Schering Pharma A G v. Barr Laboratories Inc., 91 USPQ2d 1569, 1573 (Fed. Cir. 2009), generalities or vague or non-existent guidance towards the claimed invention is insufficient to render a claim obvious; there must be some reason for the ordinary artisan to make the particular invention being claimed. Harris et al provides no reason for one of ordinary skill in the art to use its method to produce a polypeptide in authentic form as presently being claimed.

(M) Reply: As acknowledged by Appellants, there is motivation to make authentic polypeptides.

As explained above, Harris et al teaches using Granzyme B to cleave fusion proteins comprising the motif IEAD↓XG, wherein X is any amino acid (Fig 5A&D). The skilled artisan

would easily recognize that said motif comprises, as taught by Azad et al, the first two amino acids of authentic nef27, Met-Gly (pg 651, parg2, line 7, Met-Gly encoded by "ATG-GGT") and that cleavage by Granzyme B would release the authentic nef27 protein. Also, see Reply (I), above.

(N) Harris et al teaches away from the present invention because Harris et al teaches the necessity of Pl' and P2' amino acids:

> "[A]n optimal substrate for granzyme B was that spans over six subsites was determined to be Ile-Glu-Xaa-(Asp↓Xaa)-Gly, which [with] cleavage of the Asp↓Xaa peptide bond. Granzyme B proteolysis was shown to be highly dependent on the length and sequence of a substrate…" (Abstract)

Therefore, one of skill in the art would be led away from the present invention directed to a method wherein the Granzyme B cleavage site is "P4 P3 P2 P1↓", followed [by the] polypeptide of interest in authentic form. Instead, one of skill in the art following the teaching of Harris, et al., and using six peptide cleave motif for which Harris et al teaches that proteolysis is highly dependent, would be left with a polypeptide of interest with the two amino acids following the cleavage site, P 1' and P2', and would not have a polypeptide of interest in authentic form as claimed.

(N) Reply: Said asserted teachings Harris et al do not teach away from the present invention for the following reasons. First, as explained above, the sequence IEXDXG includes the Granzyme B cleavage motif, IEAD↓MG, which comprises the first two amino acids, Met-Gly, of authentic nef27. Second, regarding the length requirement for Granzyme B, Harris et al teaches:

> "Granzyme B... is absolutely dependent on extended binding of substrate for efficient catalysis. Granzyme B is not capable of cleaving the dipeptide substrate, Ac-PD-pNA or the single residue substrate, Ac-D-pNA, at concentrations as high as 4 mM. Reducing the optimal tetrapeptide, Ac-IEPD-pNA, to the tripeptide, Ac-EPD-pNA, results in a 100-fold decrease in activity…" (¶brdg pg 27367-68)
>
> and
>
> "…granzyme B is critically dependent on favorable extended interactions and is not capable of hydrolyzing amide substrates less than three amino acids in length." (pg 27372, ¶1)

Thus, the minimum length required for cleavage by Granzyme B is three amino acids and efficient cleavage occurs with four amino acids. The instant rejection cites using the motif IEAD↓MG, which is six amino acids. Thus, Harris et al does not teach away from the present invention.

(O) The present invention provides unexpected results. Compared to methods of preparing fusion proteins with other proteases known in the art, Granzyme B protease provides significant and unexpected improvement over the existing cited art.

Granzyme B is (a) more specific than other proteases and avoids cleavages in the middle of the protein of interest, (b) permits the purification of authentic forms of proteins of interest with no extraneous amino acids at the amino terminus thereby improving native confirmation, and (c) provides a more efficient cleavage than other proteases, which reduces production costs by reducing wasted uncleaved fusion protein. (Spec pg 3-5 & 62). Nothing in the cited art suggests to the skilled artisan that these goals can be accomplished using a Granzyme B protease as claimed.

(O) Reply: It is the Office's position that the recited invention does not provide unexpected results. Appellants' arguments are unpersuasive because both the specificity and efficiency of Granzyme B was known in the art, as follows.

(a) Regarding specificity, both Harris et al (Fig 2&5; Table II) and Casciola-Rosen (Table I) teach cleavage motif specificity for Granzyme B. Thus, the specificity of Granzyme B, compared to other proteases, was known in the art. Specifically, Harris et al shows that Granzyme B cleavage is optimal at motifs encompassed by $P^4$[I/V]-[E/Q/M]-[X]-[D]↓[X]-[G]$P^{2'}$ (Fig 5) and that efficient cleavage requires at least $P^4$[I/V]-[E/Q/M]-[X]-[D]$P^1$ (pg 27368, parg1). Thus, the skilled artisan would have recognized that Granzyme B is much more specific than, for example,

trypsin, which cleaves after essentially any Lys or Arg, or chymotrypsin, which cleaves after any essentially any Leu, Phe, or Tyr. Thus, unexpected results cannot be based on the specificity of Granzyme B, which was known in the art.

(b) Regarding production of authentic proteins, as described above, it was known in the art that Granzyme B cleavage is optimal at motifs encompassed by $P^4$[I/V]-[E/Q/M]-[X]-[D]↓[X]-[G]$P^{2'}$ (Harris et al; Fig 5). Thus, the skilled artisan would have recognized that any protein having a glycine at position two can be released by Granzyme B from a fusion protein comprising …[I/V]-[E/Q/M]-[X]-[D]↓([X]-[G]-protein), wherein …[I/V]-[E/Q/M]-[X]-[D]↓[X]-[G] is the Granzyme B cleavage motif, ↓ is the cleavage site, and ([X]-[G]-protein) is the authentic protein.

(c) Regarding efficiency, both Harris et al (Table II) and Casciola-Rosen et al (Table I) teach the cleavage efficiency of Granzyme B with a variety of peptide motifs. Thus, the skilled artisan would have been aware of the cleavage efficiency of Granzyme B compared to other proteases known at the time of filing. The specification fails to provide any evidence that the cleavage efficiency of Granzyme B is different, specifically more efficient, than what is taught by Harris et al and Casciola-Rosen et al. Thus, unexpected results cannot be based on the efficiency of Granzyme B, which was known in the art.

(2) Regarding the rejection of Claims 4, 6, and 41 under 35 U.S.C. 103(a) as being unpatentable over the combination of Azad et al, 1994, Harris et al, 1998, and Casciola-Rosen et al, 1999 in view of Boutin et al, 1997, Appellants provide the following arguments. These arguments are not found to be persuasive for the reasons following each argument.

(A) Claims 4-6 depend, directly or ultimately, from independent claim 1; claim 41 depends from independent claim 40. For the reasons described above, claims 1 and 40 are not obvious over

the combination of Azad, et al., Harris, et al., and Casciola-Rosen et al Accordingly, claims 4-6 and 41 are not obvious for the same reasons discussed above that claims 1 and 40 are not obvious.

(A) Reply: It is noted that Claims 4, 6, and 41, not Claims 4-6 and 41, stand rejected under 35 U.S.C. 103(a) as being unpatentable over the combination of Azad et al, 1994, Harris et al, 1998, and Casciola-Rosen et al, 1999 in view of Boutin et al, 1997.

These arguments are not found to be persuasive for the reasons set forth above regarding the rejection of Claims 1, 9-11, 16, 17, 40, 44-46, 50, and 51 under 35 U.S.C. 103(a) as being unpatentable over Azad et al, 1994 in view of Harris et al, 1998 and further in view of Casciola-Rosen et al, 1999.

(B) Boutin et al does not add to the case of obviousness against claims 1 and 40.

(B) Reply: Boutin et al is not required for the rejection of Claims 1, 9-11, 16, 17, 40, 44-46, 50, and 51 under 35 U.S.C. 103(a) as being unpatentable over the combination of Azad et al, Harris et al and Casciola-Rosen et al.

However, Claim 4 introduces the limitation that "the N-terminus of the polypeptide of interest is adjacent to the cleavage site and the penultimate amino acid at the N-terminus of the polypeptide of interest is glycine". Claims 6 and 41 introduce the limitation "wherein the polypeptide of interest is selected from the group consisting of an enzyme...".

As explained above in the reasons for rejection, Boutin et al teaches that essentially all proteins that become myristoylated begin with Met-Gly- at the N-terminus, including the enzyme calcineurin B (Table 3). Thus, Boutin et al renders obvious the production of authentic calcineurin B using the method rendered obvious by the combination of Azad et al, Harris et al and Casciola-Rosen et al.

(C) The Examiner recognizes that Harris et al, Azad et al, and Casciola-Rosen et al does not "teach preparing a protein of interest by providing a fusion protein comprising, from the N-terminal to the C-terminal, a fusion partner, a Granzyme B cleavage motif, and the protein of interest followed by contacting the fusion protein with Granzyme B, wherein the polypeptide of interest is an enzyme." (Action of April 7, 2009, p. 8). To address this deficiency, the Examiner asserts that Boutin et al teaches that, like nef27 (see Azad, et al.), essentially all proteins that become myristoylated begin with Met-Gly at the N-terminus. The Examiner further asserts that Boutin et al teaches an enzyme, Calcineurin B, that begins with Met-Gly at the N-terminus (referring to Table 3). The Examiner points out that the N-terminal Met of Calcineurin B is removed co-translationally (referring to p. 16, paragraph 6 of Boutin, et al.) The Examiner concludes that it would have been obvious to a person skilled in the art to modify the fusion protein allegedly rendered obvious by the combination of Azad et al and of Harris, et al., such that the nef27 protein is substituted with an enzyme, i.e., calcineurin B, as taught by Boutin et al Id.

The Examiner's reasoning regarding the myristoylation of polypeptides and the removal of the N-terminal methionine is not relevant to the obviousness rejection. Even assuming that the Met was present, or that the protein is myristolyated, the Examiner's only reasoning for using Boutin et al in the rejection is that one of skill in the art would be motivated to produce Calcineurin B. (Action of April 7, 2009, p. 8. and Action of June 14, 2010, p. 13). Apparently, the only reason that Boutin et al is used in the rejection is related to the fact that Calcineurin is an enzyme that, assuming the Met is counted, would have a glycine that is penultimate to the N-terminus.

(C) Reply: Appellants' summary of the instant rejection is acknowledged.

(D) These reasons do not add to the case of obviousness based upon Harris, et al., Azad, et al., and Casciola-Rosen, et al., alone, including with regard to dependent claims 4-6 and 41. With regard to independent claims 1 and 40, Boutin et al is not cited as teaching fusion proteins, any proteases cleaving fusion proteins, or the production of polypeptides using fusion proteins or proteases. Therefore, Boutin et al is irrelevant to claims 1 and 40.

Therefore, the sole fact that Calcineurin B is an enzyme would not motivate one of skill in the art combine Boutin et al with Harris, et al., Azad, et al., or Casciola-Rosen, et al.

(D) Reply: It is acknowledged, as stated above, that Boutin, et al is not needed or used for the rejection of Claims 1, 9-11, 16, 17, 40, 44-46, 50, and 51 under 35 U.S.C. 103(a) as being unpatentable over the combination of Azad et al, Harris et al and Casciola-Rosen et al.

As explained above for the instant rejection (section (9) Grounds of Rejection), "Boutin et al teach that, like nef27, essentially all proteins that become myristoylated begin with Met-Gly at the N-terminus, including the enzyme calcineurin B (Table 3). It would have been obvious to a person of ordinary skill in the art to modify the method rendered obvious by the combination of Azad et al, Harris et al, and Casciola-Rosen et al, such that the nef27 protein is substituted with calcineurin B. Motivation to do so derives from the desire to produce calcineurin B, a calcium-dependent phosphatase, using Granzyme B." Thus, the desired to produce authentic calcineurin B provides motivation to combine Boutin et al with Azad et al, Harris et al and Casciola-Rosen et al.

(3) Regarding the rejection of Claims 13-17 and 47-49 under 35 U.S.C. 103(a) as being unpatentable over the combination of Azad et al, 1994, Harris et al, 1998, and Casciola-Rosen et al, 1999 in view of Sigma Inc, 1998 or Pharmacia, Inc 1986, Appellants provide the following

arguments. These arguments are not found to be persuasive for the reasons following each argument.

(A) The Examiner acknowledges that combination of Azad, et al., Harris, et al., and Casciola-Rosen et al does not teach a method wherein the Granzyme B is immobilized and cites Sigma Inc. 1998 and Pharmacia Inc. as teaching the use of immobilized proteases. Based on that, the Examiner concludes that it would have been obvious to one skilled in the art to modify the method allegedly rendered obvious by the combination of Azad, et al., Harris, et al., and Casciola-Rosen et al to used immobilized Granzyme B.

(A) Reply: Appellants' summary of the instant rejection is acknowledged.

(B) The Examiner's conclusion is incorrect. Sigma Inc. 1998 teaches a Thrombin CleanCleave TM Kit containing Sigma's thrombin-agarose suspension used to cleave fusion proteins containing a thrombin cleavage site. Sigma Inc. 1998 further teaches that the optimal cleavage sites for thrombin are: a) P4-P3-Pro-Arg/Lys • P1 '-P2', wherein P4 and P3 are hydrophobic residues, P 1' and P2' are non-acidic residues and Arg/Lys • P1 'is the scissile bond and b) P2-Arg/Lys • P1' where P2 or P1' is glycine and Arg/Lys • P1' is the scissile bond. Pharmacia teaches sepharose coupling gels for the immobilization of ligands via a specific functional group.

(B) Reply: The fact that Sigma Inc teaches thrombin and cleavage motifs thereof is not relevant to the instant rejection. The relevant teachings of Sigma Inc are that immobilized proteases were known in the art.

(C) However, neither Sigma Inc. 1998's description of Thrombin-Agarose suspension nor Pharmacia Inc.'s description of sepharose coupling gels teaches the production of a polypeptide in

authentic form as presently claimed. Thus, the addition of neither Sigma Inc. 1998 nor Pharmacia Inc. cures the deficiency of the combination of Azad et al, Harris et al, and Casciola-Rosen et al to render obvious independent claims 1 and 40. Therefore, the combination can not render obvious dependent claims 13-17 and 47-49.

(C) Reply: As explained above, it is the combination of Azad et al, Harris et al, and Casciola-Rosen et al that teaches the production of a polypeptide in authentic form.

It is noted that Claims 13 and 47 introduce the limitation of Granzyme B in an immobilized form, Claims 14 and 48 introduce the limitation of Granzyme B immobilized via the C-terminus, and Claims 17 and 49 introduce the limitation of Granzyme B immobilized via a lysine residue. As explained above, for the instant rejection (section (9) Grounds of Rejection):

> "... the use of immobilized proteases for generating a polypeptide from a fusion protein is well-known in the art; see, for example Sigma, Inc. In addition, it was well-known that proteins can be immobilized via the N-terminus, the C-terminus, or lysine residues (Pharmacia, Inc). It would have been obvious to a person of ordinary skill in the art to modify the method of rendered obvious by the combination of Azad et al and Harris et al to used immobilized Granzyme B. Motivation to do so derives from the desire to circumvent the need to remove Granzyme B from the generated polypeptide."

Thus, Sigma Inc and/or Pharmacia Inc teach the additional limitations recited in Claims 13-17 and 47-49.

(4) Regarding the rejection of Claims 8 and 43 under 35 U.S.C. 103(a) as being unpatentable over Wan et al, 1996 in view of Bleackley et al, 1988 and further in view of Harris et al, 1998, Appellants provide the following arguments. These arguments are not found to be persuasive for the reasons following each argument.

(A) Applicants request that this rejection be reversed because the combination of Wan et al, Bleackley et al, and Harris et al is not asserted as rendering obvious independent claims 1 and

40, from which claims 8 and 43 depend. Because claims 1 and 40 are not obvious for the reasons stated above, dependent claims 8 and 43 are also not obvious.

(A) Reply: Independent Claims 1 and 40 are rejected under 35 U.S.C. 103(a) as being unpatentable over Azad et al, 1994 in view of Harris et al, 1998 and further in view of Casciola-Rosen et al, 1999. Said rejection does not require the teachings of Wan et al.

It is noted that Claims 8 and 43 introduce the limitation of producing authentic Granzyme B. The skilled artisan would have known that a fusion protein comprising a protease and a cleavage motif thereof would be cleaved by autolysis. For example, as explained for the instant rejection (section (9) Grounds of Rejection), Wan et al teaches a method for production of authentic HIV-1 protease, wherein the method uses a fusion protein comprising HIV-1 protease that proteolytically autoprocesses (pg 572, parg 2; Fig 3). However, Wan et al does not teach or mention Granzyme B. As per the rejection, it is Bleackley et al that teaches that Granzyme B is synthesized as a prepro-form, which must be processed at $^{17}$GAEE↓II$^{22}$ (Fig 1) to remove the first 20 amino acids for activation (pg 155, parg 4). Thus, it would have been obvious to make a fusion protein comprising Granzyme B protease wherein the motif GAEE↓II$^{2}$ would be replaced with the motif IEAD↓IG$^{2}$, a cleavage motif for Granzyme B (Harris et al; Fig 5). Said fusion protein would proteolytically autoprocess, thereby producing the active authentic Granzyme B protease.

Thus, Wan et al teaches a limitation introduced by Claims 8 and 43, production of an authentic protease.

**(11) Related Proceeding(s) Appendix**

No decision rendered by a court or the Board is identified by the Examiner in the Related Appeals and Interferences section of this Examiner's answer.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

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